Amendments to the Drawings:

The attached replacement sheets of drawings includes changes to Fig. 3 and replaces the original sheet including Fig. 3.

REMARKS

Claims 1-10 are pending. Applicants have cancelled claim 8 and 9 without prejudice. Applicants have added new claims11-13. Claims 1-7 and 10-13 will therefore be pending in the application.

Claim Amendments

Claims 5 and 6

Applicants have amended claim 5 to recite acyl groups that fall within the acyl general formula "R-CO-" on page 3, line 6 of the specification and to correct inadvertent and obvious typographical errors. Support for the amendments to claim 6 can be found throughout the specification, e.g., at page 4, lines 21-24.

New claims 11-13

New claim 11 is directed to formulations in which the drug is formoterol fumarate dihydrate.

New claim 12 is directed to formulations in which the drug is budesonide.

New claim 13 is directed to formulations in which there are two drugs and these are fluticasone propionate and salmeterol xinafoate, ciclesonide and formoterol fumarate dihydrate, mometasone furoate and formoterol fumarate dihydrate, or, fluticasone propionate and formoterol fumarate dihydrate.

Support for new claims 11-13 can be found throughout the specification, e.g., at page 4, lines 21-24.

Request for Clarification regarding the status of claim 7

According to the Office Action (Office Action, pages 3-4, emphasis in original):

> [A] provisional election was made without traverse to prosecute the invention of Group I, claims 1-9. Affirmation of this election must be made by applicants in replying to this Office action. **Claims 7 and 10 are withdrawn** from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicants agreed, for the sole purpose of expediting prosecution of the present application, to elect Group I, claim 1-9 for further prosecution. As indicated elsewhere in the Office Action, Applicants made the foregoing election in a telephone interview with the Examiner on September 23, 2009. At the express request of the Examiner, Applicants also provisionally elected "budesonide" as the drug.

As indicated above, Applicants elected Group I, which included claims 1-9 as originally filed. Claim 7 clearly falls within the purview of elected Group I. Claim 7 even requires the presence of budesonide. Thus, there does not appear to be any basis for the Office's withdrawing claim 7 from further consideration. Clarification and/or rejoinder of claim 7 with claims 1-6 is respectfully requested.

Request for Rejoinder of Claim 10

It is submitted that claim 10 is eligible for rejoinder with the product claims once the Office deems the product claims in condition for allowance (see MPEP § 821.04). Rejoinder of claim 10 is therefore respectfully requested.

Amendment to the Specification

As requested by the Office, Applicants have inserted the subheading "Brief Description Of The Several Views Of The Drawings" immediately before the descriptions of Figures 1-3 in the specification.

Amendment to the Drawings

According to the Office Action, the drawings are objected to because "Figure 3 is illegible." According to the specification (page 5, lines 3-7):

> FIG. 3 shows an HFA pMDI solution formulation in HFA 227. The left tube contains budesonide in HFA 227 at C=0.04% w/w. The tube in the middle contains a physical mixture of budesonide (C=0.04% w/w) and peracetylated β cyclodextrin (C=0.04% w/w) as prepared in the suspension section. The right tube contains the spray dried 1:1 complex of budesonide (C=0.04% w/w) and peracetylated β cycloxdextrin (C=0.04% w/w).

Figure 3 provided in the attached Replacement Sheet seeks to further clarify the appearance of the contents of the left, middle, and right tubes mentioned in the description above. No other substantive changes to Figure 3 have been made.

The foregoing amendments are being made for the sole purpose of expediting prosecution of the present application; and Applicants expressly reserve the right to pursue any cancelled subject matter in one or more continuing applications.

Rejections under 35 U.S.C. § 112

Claim 6 is rejected for allegedly failing to comply with the written description requirement of 35 U.S.C. § 112. The recitation of "solvates" in claim 6 appears to be the basis for the rejection (see page 6 of the Office Action). Applicants respectfully disagree with the grounds for the rejection; however, to expedite prosecution of the present application, Applicants have deleted the term "solvates" from claim 6.

Claim 6 is separately rejected for allegedly failing to comply with the enablement requirement of 35 U.S.C. § 112. The recitation of "solvates" in claim 6 again appears to be the basis for the rejection (see page 6 of the Office Action). Applicants respectfully disagree with the grounds for the rejection; however, to expedite prosecution of the present application, Applicants have deleted the term "solvates" from claim 6.

Claims 8 and 9 are rejected for allegedly failing to comply with the enablement requirement of 35 U.S.C. § 112. Applicants respectfully disagree with the grounds for the rejection; however, to expedite prosecution of the present application, Applicants have cancelled claims 8 and 9, thus rendering the rejection moot.

Rejection under 35 U.S.C. § 103

Claims 1-6, 8, and 9 are rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over **"Muller et al. (WO 2003/066031) in view of Uekama et al. ("Cyclodextrin Drug Carrier Systems," Chem. Rev. 1998, 98, pp 2045, 2048 (Table 2); and 2063),** wherein US 2005/0085445 is being used as the English language equivalent of WO 2003/066031" (Office Action, page 14, bold emphasis in original). These two references are referred to below as "Muller" and Uekama," respectively.

This is respectfully traversed.

[1] Claim 1 is directed to an HFA drug formulation that includes a partially or fully acylated alpha (α), beta (β) or gamma (γ) cyclodextrin.

[2] Muller

Muller et al concerns metered-dose aerosol inhaler stabilised pharmaceutical HFA suspension formulations comprising a native or modified cyclodextrin. There is no disclosure of acylated cyclodextrins. Rather, Muller focuses heavily on hydroxyalkyl modified cyclodextrins; see Muller at page 2, paragraph 0024:

> The cyclodextrine used according to the invention can be a native or modified α-, β-, or γ-cyclodextrine. Examples of modified cyclodextrines are hydroxymethyl-α-cyclodextrine, hydroxyethyl-α-cyclodextrine, hydroxypropyl-α-cyclodextrine, α-cyclodextrine butyl sulphonate, α-cyclodextrine butyl fluoride and sulphobutyl-α-cyclodextrine; hydroxymethyl β-cyclodextrine, hydroxyethyl-β-cyclodextrine, hydroxypropyl-β-cyclodextrine, β-cyclodextrine butyl sulphonate, β-cyclodextrine butyl fluoride and sulphobutyl-α-cyclodextrine as well as hydroxymethyl-γ-cyclodextrine, hydroxyethyl-γ-cyclodextrine, hydroxypropyl-γ-

> cyclodextrine, γ-cyclodextrine butyl sulphonate, γ-cyclodextrine butyl fluoride and sulphobutyl-γ-cyclodextrine.

In fact, Muller appears to use hydroxyalkylated cyclodextrins in **all** of his exemplified formulations.

[3] Uekama

Uekama is a review article entitled "Cyclodextrin Drug Carrier Systems." Uekama describes cyclodextrin derivatives (including acylated cyclodextrins); however, Uekama does not refer at all to formulations that are to be delivered to the lung *via* an inhaled aerosol composition (*cf*: Muller discussion above).

Uekama discloses a table ("Table 1" in Uekama at page 2047) that includes "[t]ypical examples of the pharmaceutically useful β-cyclodextrin derivatives" (Uekama, page 2046). In Uekama's Table 1, the derivatives are "classified into hydrophilic, hydrophobic, and ionic derivatives" (Uekama, page 2046). "Hydroxyalkylated cyclodextrins," i.e., the type of cyclodextrin that is used in all of Muller's exemplified formulations, are classified by Uekama as "**hydrophilic** derivatives" (see Uekama's Table 1 at page 2047, emphasis added). On the other hand, "acylated cyclodextrins," which are required by the present claims, are classified by Uekama as "**hydrophobic** derivatives" (see Uekama's Table 1 at page 2047, emphasis added).

[4] The Supreme Court discussed the requirements for making rejections under 35 U.S.C. 103 in *KSR Intern. Co. v. Teleflex Inc.* 127 S.Ct. 1727, 1742 (2007, bolded, underline emphasis added).

> Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit. *See In re Kahn*, 441 F.3d 977, 988 (C.A.Fed.2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the

> legal conclusion of obviousness"). As our precedents make clear, however, the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.
>
> When it first established the requirement of demonstrating a teaching, suggestion, or motivation to combine known elements in order to show that the combination is obvious, the Court of Customs and Patent Appeals captured a helpful insight. See *Application of Bergel*, 48 C.C.P.A. 1102, 292 F.2d 955, 956-957 (1961). As is clear from cases such as Adams, **a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art**. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, **it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does**. This is so because **inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known**.

Thus, a claim is not proved obvious merely by showing that the elements of that claim can be found in the prior art. Rather, the Office must articulate some reason as to why a person of ordinary skill in the art, at the time of the invention, would have combined the elements in the manner required by the claim.

[5] Here, claim 1 is directed to an HFA drug formulation that includes a partially or fully acylated alpha (α), beta (β) or gamma (γ) cyclodextrin. As explained in the specification, an HFA (hydro fluoro alkanes) or mixtures thereof, are used, e.g., as propellants in inhalation delivery devices (e.g., pressure metered dose inhalers). Muller et al concerns metered-dose aerosol inhaler stabilised pharmaceutical HFA suspension formulations comprising a native or modified cyclodextrin. There is no disclosure of acylated cyclodextrins in Muller. Uekama et al report cyclodextrin derivatives (including acylated cyclodextrins); however, Uekama does not refer at all to formulations that are to be delivered to the lung *via* an inhaled aerosol composition. Thus, the Office has only identified elements of the present claims in two unrelated disclosures,

but has not articulated any reason why one would have combined these two unrelated disclosures.

[6] Even if one would have been led to the prior art of record, it still would not have been obvious to have made the modifications needed to arrive at the claimed formulations. As explained above, Muller focuses heavily on hydroxyalkyl modified cyclodextrins, which according to Uekama, are **hydrophilic** in nature. In fact, Muller appears to use hydroxyalkylated cyclodextrins in **all** of his exemplified formulations. In contrast, the claims require the presence of acylated cyclodextrins, which according to Uekama, are **hydrophobic** in nature. It is therefore submitted that one would not have combined and modified Muller and Uekama in the manner suggested by the Office, because doing so would have required that one ignore outright Muller's clear preference for hydrophobic cyclodextrins. If anything, the teachings of Muller and Uekama would have led one of ordinary skill in the art away from making the modifications needed to arrive at the claimed formulations.

[7] In summary, Applicants therefore respectfully request that the rejection be reconsidered and withdrawn because the Office, at most, has only identified the elements of the present claims in three unrelated disclosures, but has not articulated any reason why the claimed kits and pharmaceutical compositions would have been obvious at the time that the present application was filed.

The fee in the amount of $130 for the One Month Extension of Time is being paid concurrently herewith on the Electronic Filing System (EFS) by way of a Deposit Account authorization. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No.: 06275-0512US1/101287-1P US.

Respectfully submitted,

Date: February 1, 2010

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